Promoting Objectivity in NINDS Phase III Clinical Trials: Avoiding Financial Conflicts of Interest

Federal and private sector investment in academic research has led to a vibrant culture of entrepreneurial science. Academic investigators hold intellectual property and develop close relationships with the private sector in order to accelerate the translation of discoveries into potential therapies for patients. These activities support the mission of the National Institute of Neurological Disorders and Stroke (NINDS) to reduce the burden of neurological disease. However, such arrangements also have the potential to create concurrent professional and financial interests in a research project which could be considered a conflict of interest (COI). Although the existence of a financial COI should not be construed as evidence of wrongdoing, it may lead an independent observer to reasonably question whether professional decisions are influenced by personal financial considerations.

Protecting the safety of human subjects, the credibility of data, and the public's trust in clinical trials are goals shared by the clinical research community and the NINDS. Financial COI that have the potential to diminish investigator objectivity may compromise these shared goals. For this reason, the clinical research community has widely recognized that financial interests related to clinical trials deserve special attention[1,2,3,4].

In 1995, the Department of Health and Human Services (DHHS) issued regulations[5] to promote objectivity in research. The NIH released Notices in 2000 and 2004 to remind applicants of the financial conflict of interest requirements for all NIH-supported institutions. In 2004, the DHHS Office for Human Research Protections (OHRP) released guidance on Financial Relationships and Interests in Research Involving Human Subjects[6]. The NINDS recognizes the importance of these issues, and will devote special attention to the disclosure and management of financial COI in its Phase III clinical trials. At a minimum, the NINDS believes that financial COI related to the trial should be disclosed during the informed consent process and in any trial-related publications and presentations.

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[1] Association of American Medical Colleges Task Force on Financial Conflicts of Interest in Clinical Research. 2003. Protecting subjects, preserving trust, promoting progress II: principles and recommendations for oversight of an institution's financial interests in human subjects research. Acad Med. 78(2):237-45.

[2] Association of American Medical Colleges Task Force on Financial Conflicts of Interest in Clinical Research. 2003. Protecting subjects, preserving trust, promoting progress I: policy and guidelines for the oversight of individual financial interests in human subjects research. Acad Med. 78(2):225-36.

[3] Association of American Universities Task Force on Research Accountability. 2001. Report on Individual and Institutional Financial Conflict of Interest. http://www.aau.edu/research/COI.01.pdf

[4] Council on Governmental Relations: Recognizing and Managing Personal Financial Conflicts of Interest, "Approaches to Developing an Institutional Conflict of Interest Policy" http://www.cogr.edu/files/publications_Conflicts.cfm; and "Recognizing and Managing Personal Conflicts of Interest" http://www.cogr.edu/docs/COIFinal.pdf (Winter 2002)

[5] 42 CFR Part 50, Subpart F "Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding is Sought " and 45 CFR Part 94.1 "Responsible Prospective Contractors," published in the July 11, 1995 issue of the Federal Register (Volume 60, Number 132, Page 35809)

[6] http://www.hhs.gov/ohrp/humansubjects/finreltn/fguid.pdf; "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection," published in the May 12, 2004 issue of the Federal Register (Vol. 69, No.92, Page 26393).

The NINDS guidelines promote subject safety, study credibility, and public trust in neurological research without stifling translation of promising pre-clinical discoveries.

NINDS Financial COI Guidelines

The NINDS requires that Phase III clinical trial applications contain a written policy on financial COI within the protocol which will apply to all investigators and other individuals with critical roles in the study. The financial COI policy will be developed by the investigative group. The NINDS does not specify exactly what policy a given study should develop, however, at a minimum the policy should include the four elements described below. Investigators are encouraged to review study policies used in other NIH trials, and a sample policy developed by NINDS www.xxx.xxx. NINDS program staff will also be available to provide guidance to investigative groups.

The peer-review committee reviewing the trial application will comment on the investigators' plan for addressing financial COI. In addition, the financial COI policy for the study must be approved by the trial's oversight monitoring boards and the NINDS prior to subject enrollment in the trial.

The investigative group should develop a financial COI policy that:

1) **Defines the terms "investigator" and "significant financial interest"**
   - Federal regulations[7] provide a minimum standard for significant financial interests of Investigators. These regulations define "Investigator" as the principal investigator and any other person who is responsible for the design, conduct, or reporting of research funded by the Public Health Service (PHS), or proposed for such funding. With regard to financial COI, the term "Investigator" includes the investigator's spouse and dependent children.
   - The same federal regulations define "significant financial interest" as anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options or other ownership interests); and intellectual property rights (e.g., patents, copyrights and royalties from such rights). Not included in the regulatory definition of significant financial interests are
      1) remuneration from the applicant institution;
      2) ownership interests in the institution, if the institution is an applicant under the SBIR program;
      3) income from seminars, lectures, or teaching engagements sponsored by public or nonprofit entities;
      4) income from service on advisory committees or review panels for public or nonprofit entities;

[7] 42 CFR Part 50, Subpart F "Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding is Sought " and 45 CFR Part 94.1 "Responsible Prospective Contractors," published in the July 11, 1995 issue of the Federal Register (Volume 60, Number 132, Page 35809)

5) an equity interest that when aggregated for the investigator and the investigator's spouse and dependent children, meets both of the following tests; does not exceed $10,000 in fair market value, and does not represent more than a five percent ownership interest in any single entity; or
6) salary, royalties, or other payments that when aggregated for the investigator, the investigator's spouse and dependent children over the next twelve months, are not expected to exceed $10,000.

- At a minimum, grantee institutions are responsible for complying with Federal regulations at 42 CFR Part 50, Subpart F and 45 CFR Part 94.1. However, institutions have the option to adopt stricter policies than are required in the Federal regulations, and some institutions have done so. For multi-center clinical trials, investigative groups should consider the financial COI policies of the participating institutions when they are developing a standard financial COI policy for the clinical trial.

2) **Includes a procedure to prospectively identify significant financial interests that present financial COI for investigators prior to subject enrollment in the trial.** The procedure should address how to identify potential financial COI that arise later, during the conduct of the clinical trial or analysis of the results. The procedure should also include a plan to securely store records related to disclosure of financial interests.
   - The investigative group may designate the responsibility of carrying out the procedure to identify and manage financial COI to another group (for example, to a subcommittee of the clinical trial Steering Committee).
   - The NINDS considers voluntary disclosure of significant financial interests by investigators an acceptable method to identify potential financial COI.
   - To the extent possible, the need for full and open disclosure should be balanced with respect for the confidentiality of financial information.

3) **Describes actions to be taken if a financial COI is identified.** The investigative group should propose strategies to manage or eliminate the financial COI. The investigative group may wish to consider strategies such as:
   - Changing the role(s) of the conflicted investigator/individual in the design, conduct and analysis of the trial
   - Reducing or restructuring the financial arrangements
   - Eliminating the financial COI by eliminating the financial arrangement that creates the conflict, or by limiting the participation of a conflicted investigator.
   - In some cases, the investigative group will evaluate the actions taken by local institutions to manage the financial COI and determine whether the actions are sufficient with regard to the financial COI policy developed for the trial.

   The NINDS expects that any on-going financial COI related to the trial will be disclosed during the informed consent process and in trial-related publications and presentations.

4) **Includes a process to inform the NINDS Program Official of a real or perceived fCOI and the proposed management strategy. The Program Official, in**

consultation with NINDS Clinical Trials Group staff, will make the final determination regarding the proposed management strategy.

- If the NINDS Program Official becomes aware of a financial COI that has not been identified and managed through the clinical trial's financial COI procedures, the NINDS will take action to manage or eliminate the conflict.

In some cases, an investigator may wish to retain significant financial interests that present a financial COI in the clinical evaluation of an intervention. If the investigative group cannot identify a means to effectively manage the conflict or an alternative investigator/individual capable of conducting the clinical evaluation, NINDS program staff will help the investigative group explore other suitable means to evaluate the intervention in clinical trials. For example, the intervention may be tested by independent investigators in one of the NINDS clinical trial networks, such as the NINDS Clinical Research Collaboration, or through a contract mechanism with an independent organization. In general, the NINDS expects that an individual with on-going significant financial interests related to the trial will be permitted to participate as an investigator only in compelling circumstances, as recommended by the Association of American Medical Colleges. If an individual with a financial COI does participate as an investigator in the trial, the NINDS expects that the existence of the financial COI will be disclosed in the informed consent process and in all trial-related publications and presentations.

In summary, the NINDS will work with the clinical research community to promote the safety of human subjects, the credibility of the data, and the public's trust in clinical trials. Investigative groups conducting NINDS-sponsored clinical trials are expected to develop policies that help to avoid the perception that the study design, conduct, data analysis or interpretation was biased by financial interests. The NINDS will take an active role in ensuring that these guidelines are followed and retains the authority for final approval of clinical trial financial COI policies and proposed conflict management strategies.

Additional information:

For questions about these guidelines, please contact: (Contact person)

The National Institutes of Health (NIH) Office of Extramural Research Conflict of Interest website provides additional information on NIH policies regarding financial conflict of interest. http://grants.nih.gov/grants/policy/coi/index.htm

The Food and Drug Administration (FDA) provides a guidance document on "Financial Disclosure by Clinical Investigators," available at http://www.fda.gov/oc/guidance/financialdis.html.